RESPONSE TO COMMENT ON VISTISEN ET AL.

A Validated Prediction Model for End-Stage Kidney Disease in Type 1 Diabetes. Diabetes Care 2021;44:901–907

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We would like to thank Østergaard et al. (1) for their perspective on our article (2), which includes a suggestion for using lifetime prediction models to estimate disease-free life expectancy. The lifetime prediction models previously published are primarily based on Cox proportional hazards models including age as timescale (3). We have used Poisson models that facilitate the inclusion of multiple timescales such as age and diabetes duration. Both modeling approaches estimate a hazard function for the event of interest as well as for the competing event of death, and with both approaches these hazard functions can be used to estimate lifetime risk and disease-free life expectancy.

As pointed out by Østergaard et al., risk prediction should ideally cover a long time horizon, and in that sense estimating lifetime risk may seem attractive. Models predicting diseases in the future assume current risk factor levels of the patient, such as blood pressure, kidney function, and lifestyle, to remain constant over time. However, health status is a nonstatic entity with changes driven by individual behavioral choices and by temporal changes in incidence of disease, associated risk factors, and treatment regimens that may alter the current associations between risk factors and diseases. Lifetime risk models either assume no future underlying calendar time trend in disease rates or make untestable assumptions about such trends. In our study, we found model calibration to be insufficient beyond 5 years. Extending our model into a lifetime risk model will not improve calibration but rather introduce more uncertainty around the estimated risk. Current lifetime models still need to demonstrate good calibration beyond 10 years of follow-up (3–5).

Østergaard et al. advocate that lifetime prediction models for end-stage kidney disease will more accurately illustrate the potential for preventive treatment. However, this is only true if the risk of end-stage kidney disease with and without treatment can be estimated with enough precision. We acknowledge that disease-free life expectancy may improve risk communication to especially younger patients who have low absolute risk within a short time period. However, rather than providing an uncertain estimate of lifetime risk, comparing the patient's cumulative risk within a short time period to a reference patient with ideal levels of risk factors seems a better alternative.

It has been claimed that the lifetime risk models may spot unfavorable prognosis at much younger age than risk models for a shorter time horizon (3). Although, this approach may facilitate preventive treatment earlier, it also carries a potential risk of overtreatment. Lifestyle interventions are likely beneficial, but medical interventions are to some degree associated with risk and should only be initiated based on a valid estimate of their benefits.

All modeling approaches have limitations and are useless in clinical practice if risk is estimated with low precision. Advancements within this field should focus on improving discrimination and calibration of prediction models. Both by including various sources of health data and by allowing for high-level interactions between predictors to better accommodate the heterogeneity in disease development among patients.

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References

1. Østergaard HB, van der Leeuw J, Visseren FLJ, Westerink J. Comment on Vistisen et al. A validated prediction model for end-stage kidney disease in type 1 diabetes. Diabetes Care 2021; 44:901–907 (Letter). Diabetes Care 2021;44e140
2. Vistisen D, Andersen GS, Hulman A, et al. A validated prediction model for end-stage kidney disease in type 1 diabetes. Diabetes Care 2021; 44:901–907
3. Kaasenbrood L, Bhatt DL, Dorresteijn JAN, et al. Estimated life expectancy without recurrent cardiovascular events in patients with vascular disease: the SMART-REACH model. J Am Heart Assoc 2018;7:e009217
4. Hippisley-Cox J, Coupland C, Robson J, Brindle P. Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database. BMJ 2010;341:c6624
5. Lloyd-Jones DM, Wilson PW, Larson MG, et al. Framingham risk score and prediction of lifetime risk for coronary heart disease. Am J Cardiol 2004;94:20–24